Introduction: Importance of Categorization for Risk Assessment and Risk Management

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ABSTRACT

Categorized of traditional chemicals has been an important tool for purposes of testing, read across/Structure-Activity Relationships (SAR), and hazard assessment. Not only has this aided in conducting assessments with limited data and reducing the amount of testing required, it has helped promote the design, development, and application of safer chemicals and processes. This latter consideration then has an impact upon the potential risk management tools that would be used to address the chemical. These benefits are also those that are anticipated from a categorization scheme for manufactured nanomaterials. The categorization of manufactured nanomaterials is a goal for many but still in its infancy. Categorization of manufactured nanomaterials will improve risk assessments because it will help reduce uncertainties in both hazard assessments and exposure assessments, decrease the amount of data needed for individual manufactured nanomaterials. This will support more targeted risk management approaches for different types of manufactured nanomaterials.

Session 1

OECD member countries' approaches to develop or use concepts of grouping, equivalence and read-across based on physical-chemical properties (GERA-PC) of nanomaterials for their hazard assessment in regulatory regimes

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ABSTRACT

This lecture will give a snapshot of OECD member countries' approaches to develop or use concepts of grouping, equivalence and read-across based on physical-chemical properties (GERA-PC) of nanomaterials for their human health and ecosystem hazard

assessment in regulatory regimes, based on the results of a questionnaire-based survey conducted by the WPMN from October to December 2013.

By 3 December 2013, thirteen (13) responses to the questionnaire were received from eight OECD member countries, one regional organisation, and one OECD organ, namely, Australia, Canada, Denmark, Germany (three responses), Japan, Switzerland, the United Kingdom (UK), the United States (US), the European Union (EU), and the Business and Industry Advisory Committee to the OECD (BIAC, two responses).

Four member countries and one regional organisation responded that GERA-PC concepts were either in use or being prepared for use in hazard assessments in their regulatory regimes. Six member countries and one regional organisation reported various R&D activities aimed at supporting the development of GERA-PC concepts for regulatory purposes.

Additional responses were provided, addressing needs and challenges in the development and regulatory implementation of GERA-PC concepts as well as views on the limitations of, and alternatives to, those concepts. These responses were 'mapped' to a limited number of 'issues' such as: (1) Need for scientific knowledge; (1.1) Mechanistic understanding; (1.2) Comprehensive and reliable data-sets with standardised testing methods; (2) Technical challenges; (2.1) Sample preparation and material characterisation; (2.2) Dealing with surface modifications/properties; (3) Need for Regulatory Implementation; and (4) Other suggestions.

Development of a Classification Scheme under the Canada-United States Regulatory Cooperation Council Nanotechnology Initiative

Brad Fisher
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Environmental Protection Agency, United States

ABSTRACT

Prime Minister Harper and President Barack Obama announced the Canada-US Regulatory Cooperation Council on February 4th, 2011 to increase regulatory transparency and coordination between both countries in various areas, including nanomaterials.

The RCC Nanomaterials Work Plan is now complete and both Canada and the US are implementing the new approaches and lessons learned in risk assessments of

nanomaterials. The focus of this presentation will be on the approach to the Priority Setting Work Element of the Work Plan. The objective of this Work Element was to provide consistency and clarity in risk assessments through the development of a Classification Scheme. This Classification Scheme will be presented and explained to participants through discussion on the rationale behind its creation, how it was developed, its applicability and implementation in both countries and path forward. Further, participants will be invited to provide their feedback and consider the development of classes/categories from an international perspective.

EU REACH perspective of categorization, grouping and read-across

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ABSTRACT

REACH is the European Union Regulation on chemicals and their safe use (EC 1907/2006). It entails the elements of Registration, Evaluation, Authorisation and Restriction of chemicals, and entered into force on 1 June 2007. Although REACH does not explicitly addresses nanomaterials, it implicitly governs these as they fall within the definition of substance under this regulation. Currently, based on concerns from the European Parliament and Council, REACH is undergoing a review in the context of nanomaterials. This is to ensure that nanomaterials are sufficiently addressed by the regulation and their safe use can be demonstrated. This work has identified a need to find pragmatic and scientific justified approaches for categorise and group nanomaterials to minimise e.g. unnecessary animal testing and cost for industry. However, such approach must not compromise on safe use of these materials on the European market.

Under REACH the registrants have the possibility to use read-across, grouping and categorisation to bridge data gaps when conducting their hazard characterisation. Under the EU regulatory framework, existing approaches for grouping (categorisation) of conventional substances is foremost based on structural similarity and physicochemical properties as a first step. As a next step the read across hypothesis needs to be further strengthened with data of effects on human health and the environment that illustrates a similarity in behaviour. Considerations has been given by EU Member States on how a justification for a

scientifically robust read-across for nanomaterials could look like when it is done to fill data gaps as part of hazard characterisation of the substance;

· Consider the quality of the (experimental or modelled) data used in the rationale in a transparent manner

· Terminology and purpose are important and therefore, clarify the purpose and boundaries of the read-across justification

· Solubility is a key parameter for toxicity but can be affected by coating and surface treatments

· Although exposure is part of REACH data requirements and to some extent can be used to waive certain tests the group agreed that "no exposure" argument has very limited use in a justification for read-across.

These initial discussions at EU level for how read-across, grouping and categorisation of nanomaterials and forms thereof can look like will be presented and consideration from the participants will be welcomed.

Highlights of the OECD Meeting on Nanomaterials Physical-Chemical Parameters: Measurements and Methods

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ABSTRACT

In June 2014 the OECD Meeting on 'Nanomaterials Physical-Chemical Parameters: Measurements and Methods' was held in Washington. About 40 experts from member countries and Industry were present to assess the methods applied for testing the physicochemical endpoints in the OECD-WPMN testing programme. The aim of the meeting was to assess the applicability of the methods used for the specific nanomaterials as well as their general applicability, and provide recommendations for potential modifications of OECD Test Guidelines as well as the need to develop new OECD Test Guidelines.

In preparation of the meeting and to build further on the experience from the sponsorship programme and the expertise of the experimenters and other physical-chemical

and metrology experts the submitted physicochemical data from the OECD-WPMN testing programme were assessed by these experts partly prior to the meeting.

During meeting the experts present were able to determine very concrete recommendations to the OECD WPMN for modifying existing and developing new test guidelines for Nanomaterials. In this lecture and overview of the high lights of the OECD Meeting on Nanomaterials Physical-Chemical Parameters: Measurements and Methods will be presented.

Novel properties as an organizing concept for categorizing engineered nanomaterials for regulatory purposes

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ABSTRACT

The observation that some materials exhibit properties at the nanoscale that are different from the properties observed for bulk materials is at the very heart of many applications of nanomaterials that take advantage of these novel properties. We propose that one basis of a nanomaterial categorization scheme should be the novel properties exhibited by, and often specifically exploited in, engineered nanomaterials (ENMs). Such novel properties are responsible for both the purposeful interactions that drive performance of engineered nano materials as well concern and investigation with regard to collateral nanomaterial environment, health and safety (nanoEHS) concerns. These properties will drive interactions and transformations within environmental compartments and biota, and they will be the basis of decisions to develop and utilize, or abandon, individual ENMs. As such, this categorization would orient the discussion toward real world decisions on ENMs.

Practically speaking, the performance of ENMS is what will drive their adoption and utilization in applications. The criteria utilized in determining which materials to develop and utilize are performance based, and the performance will often be related to the effective harnessing of these novel properties.

Categorizing materials according to novel property allows orientation of discussions in terms of the actual decisions being made regarding these materials. Which photocatalyst is the best one to utilize? What material responds to the most finely tuned frequency of (drug delivery activation stuff)? What driver of the analyses and research. Decisions about which material to use will entail material comparisons based on performance, based on successful exploitation of the novel properties. Decisions about green chemistry approaches will also

center around optimizing performance while controlling the properties that create undesirable by-products or impart collateral damage upon release. Decisions about modelling material behavior and mode of action, and translating these into regulatory action, will be based exposure and hazard potentials driven by the uniquely nano-scale properties interacting with the environmental and biological receptors.

Under this schema, some materials (e.g. TiO2) would fit into multiple novel property categories (e.g. photocatalytic activity and UV absorption), which is appropriate because in those cases it is likely that multiple different attributes of the material must be considered separately from a risk perspective, and may correspond to different decision contexts with regard to material development, use and management.

Bridges Implication and Application Discussions and Datasets.

It so happens that mechanistic understanding of these novel properties will likely be critical to predicting their behaviour not only in the engineered systems in which they are being designed to perform, but also within the natural systems that will be the ultimate sink / receptors / for released nanomaterials and their transformation products.

Categorizing materials according to novel property ridges the discussion of what the nanomaterials are being utilized to DO in the first place with consideration of what collateral impacts may be expected, which is important both mechanistically and practically.

If the same data categorization schemata can be utilized to answer questions that inform decisions about performance (which material absorbs the widest spectrum of light?) as well as decisions about assessing and managing risks (which material generates the most net reactive oxygen species?), we can hope that the property---based categorization could serve as a common language to facilitate discussions across the application vs. implication divide. Longer term, datasets captured within this schema could be more interoperable across the application/implication divide, opening the possibility to find efficiencies by linking previously disparate datasets.

Account for Complexity.

A focus on novel properties may incorporate the critical issue of complexity into categorization of materials, allowing for the development of categories of what can be expected in terms of important transformation reactions. Materials with specific antimicrobial activity may transform similarly in similar surrounding media.

In this regard, traditional methods of categorizing materials in terms of similar core composition, for example, may align and compliment a categorization schema that focuses on novel property.

List of proposed examples.

For the purposes of beginning a discussion, we list here some novel properties of materials that could be used to categorize materials. Note that some nanomaterials may be represented in multiple categories.

- Catalysis
- Redox properties
- Photoactivity
- Mechanical strength
- Antimicrobial properties
- Adsorption
- Semiconductor and florescent properties (quantum confinement and bandgap)
- Magnetic properties
- Shape (e.g., cavities for programmable drug delivery or hydrogen storage)
- Heat conductivity/ Insulation
- Optical properties (UV block, transparency)
- Superconduction

Novel techniques for toxic nanoparticle categorization

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ABSTRACT

The unique properties of NPs can have adverse bio-impact. The safe utilization of nanotechnology governing environmental health and safety is a multidisciplinary task that goes beyond the traditional risk assessment procedures. One approach for countering the impacts is to probe the number of newly emerging NPs and their wide range of properties by using a high-throughput screening platform that utilizes NP libraries exhibiting a range of compositions and combinatorial properties to study their relationship to a specific injury responses as well as exploiting computational methods to assist in the establishment of quantitative safer-by-design approaches. The development of conceptual paradigms in environmental and health assessment has been recognized that the physicochemical properties of engineered NPs play a key role in their fate and transport, human and environmental exposure, and hazard generation. As an attempt, 24 metal oxide NPs from different groups and periods from the periodic table was chosen and assessed based on their potential overlap of conduction band energy and cellular redox potential (-4.12 to -4.84 eV). The assessment of the cellular response was performed using mammalian cell line, sea organism (zebra-fish) and bacteria 1-3. The reasonable correlation observed within these

wide test models provided clear evidence that these 24 metal oxide nanoparticles could be categorized to toxic or non-toxic according to their specific physicochemical properties. Results acquired from these models showed (1) conduction band energy overlapping with the redox potential in the cellular interior are toxic (2) metal oxide nanoparticles ionizing in the cells and chelating with the biological species are toxic (3) metal oxide nanoparticles having hydration energy > -70eV are toxic. The acquired knowledge in this area (through extensive categorization of the nanoparticles) will offer new opportunities to remediate environment through multi-disciplinary research between several fields of science.

1. H. Zhang, Z. Ji, T. Xia, H. Meng, C. Low-Kam, R. Liu, S. Pokhrel, S. Lin, X. Wang, Y.-P. Liao, M. Wang, L. Li, R. Rallo, R. Damoiseaux, D. Telesca, L. Madler, Y. Cohen, J. I. Zink, A. E. Nel, Use of metal oxide nanoparticle semiconductor properties and band gap to develop a predictive paradigm for the oxidative stress injury and acute toxicological potential in cells and the murine lung, ACS Nano, 2012, 6(5), 4349–4368.

2. S. Lin,Y. Zhao, Z. Ji, J. Ear, C. H. Chang, H. Zhang, C. Low-Kam, K. Yamada, H. Meng, X. Wang, R. Liu, S. Pokhrel, L. Mädler, R. Damoiseaux, T. Xia, H. A. Godwin, S. Lin, A. E. Nel, Screening to reveal the mode-of-action of metal oxide nanoparticles toxicity in zebrafish embryos, Small, 2013, 9(9-10), 1776-1785. 3. C. Kaweeteerawat, A. Ivask, R. Liu, H. Zhang, C. H. Chan, C. Lowkam, H. Fischer, Z. Ji, S. Pokhrel, Y. Cohen, J. Zink, L. Mädler, P. Holden, A. Nel, H. Godwin, Toxicity of metal oxide nanoparticles in bacteria correlates with conduction band energy and hydration energy, Eviron. Sci. Technol. 2014, Submitted

Keynote lecture: "The use of Alternative Testing Strategies to Advance Risk Analysis of Nanoscale Materials"

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ABSTRACT

The Emerging Nanoscale Materials Specialty Group (ENMSG) of the Society for Risk Analysis (SRA) recently held a workshop to investigate the use of alternative testing strategies (ATS) for exposure and risk analyses of nanoscale materials (http://www.srananoworkshop.org). The workshop convened a diverse group of international experts to discuss how current and evolving in vitro assays might be applied in a "multiple models" approach to inform risk assessments of novel nanoscale materials, including assessing hazard, potency and exposure potential. Participants examined the availability and applicability of novel ATS methods for a multiple-models approach to toxicity, environmental and exposure analyses of emerging nanoscale materials (ENM) in the risk analysis paradigm. The presentation will describe the findings and recommendations of the expert deliberation and elaborate shared strengths and gaps in support of weight-of-

evidence (WOE) methods that rely on ATS to inform context-specific assessment and management decisions for novel nanoscale materials. Recommendations and guidance for using ATS in hazard characterization and risk assessment for those decisions will be shared.

Grouping of Nanomaterials for Health Assessment: Genotoxicity

Maria Donner
DuPont, Business and Industry Advisory Committee

ABSTRACT

This presentation summarizes the outcome of the WPMN Expert Meeting on Genotoxicity of Manufactured Nanomaterials (November 18-19, 2013, Ottawa, Canada) and places it in the context of current requirements and guidelines for assessment of genotoxicity endpoints. A grouping of nanomaterials (NMs) is a logical next step, and would be advantageous for identifying potential genotoxic properties and human health hazards that might be associated with NMs. However, it is premature to attempt this based on the currently available genetox data, based on their inconsistency. Positive results are almost the rule in the in vitro comet assay and in a limited array of other genetox tests. On the other hand, data from in vivo experiments are often contradicting and do not necessarily support the in vitro findings. It has been generally agreed that at the current OECD testing guidelines should be evaluated and adapted as appropriate for NMs. Any revision must be carefully considered and data-based, as well as preceded by expert opinion on how the unique physicochemical properties of NMs will be taken into account, and how to proceed with identification of critical similarities and differences. A successful categorization will facilitate these distinctions, and provide an aid for selection of exposure and testing conditions, and the construction of a training set to use for computational approaches. This categorization is considered to more likely to be driven by other aspects of NMs, such as physicochemical properties, than on genotoxicity.

Health effects of nanomaterials state of the art and their regulatory implications

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ABSTRACT

The last 15 years the majority of nano-toxicity research is focusing on in vitro systems.

Many questions have been raised regarding the quality of the in vitro nano-tox research due to disregarding transformation of the NP's under experimental conditions and lack of thorough quality control. Thus, an understanding of the relationship between the physical and chemical properties of the nanostructure and their in vivo behavior needs to provide a basis for assessing nano-toxicity and lead to predictive models for nano-toxicity assessment.

The WPMN has in response to a increasing number of publications on the possible implications of nanomaterials on human health, started in their exploratory phase of its existence the "Sponsor-projects-program". Since the start of WPMN initiatives like the Nano-Safety-Cluster (NSC) of the EU and similar programs in the US (EHS-NNI) and other OECD-WPMN members (i.e. Japan, Australia, Canada, Korea) have been funding research manifold over the budget of the Sponsor-project. Industry has stepped up their participation the most recent being the Nano-release project.

Due to these on-going efforts many studies have become available of in vivo NP-exposure. Predominantly based on inhalation as exposure route, which is perceived as the most critical route of exposure.

This keynote on the health impacts of nanomaterials will present recent results in vivo work and explore their implications for regulatory purposes.

Example of the Grouping of Nanomaterials for Health Assessment in a National or International Regulatory Context. How to extend/verify the Concept: "Taquann" whole body inhalation system for speeding up the toxicity studies for categorization of manufactured nanomaterials

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ABSTRACT

Using the Mitsui MWNT-7 as a de facto standard multi-wall carbon nanotube for fiber-type nanomaterial toxicity studies, we first monitored its mesotheliomagenic potential by the intraperitoneal injection model of p53 heterozygous mice (J Tox. Sci. 33:105-16, Cancer Sci. 103:1440-4, 2012). These studies suggested that non-granulomatous chronic

inflammatory microlesions are closely related to the “frustrated phagocytosis” originally proposed in the past for the asbestos carcinogenesis.

In general, however, there is no pre-existing toxicity data on a new nanomaterial; its toxicity should be studied in a case-by-case basis. Meanwhile, since inhalation is the major route of exposure for humans, the whole body inhalation exposure study is the first choice for assessing its “hitherto unknown” toxicity.

We adopted MWNT-7 as the first sample to develop a new whole body inhalation system. A major problem with generating MWNT-7 aerosol was the agglomerates and aggregates in its bulk sample. We developed a method to generate aerosol of highly-dispersed MWNT-7 single fibers without aggregate/agglomerate and a small scale inhalation system for it (Taquann Method and Taquann Direct Injection System, J Tox. Sci. 38:619-628, 2013). Aerosol in the inhalation chamber was composed of single fibers of same size distribution to the fibers in the original sample. Fibers of same length distribution were found in mouse lung, and histology showed no aggregates/agglomerates and no granulomatous changes. The fibers were also found in the microscopic lesions located on the surface of parietal pleura; the microlesions were similar to what we monitored in the intraperitoneal injection studies.

The Taquann system is relatively cheap, simple and easy to operate, and is a sealed system easy to keep the facility clean. There is no sample loss after liquid phase filtration so that this system is ideal for testing the new nanomaterials of low-product-volume. The system can be applied to various types of nanomaterial; we have tested TiO2 nanoparticles to gain highly dispersed aerosol.

In conclusion, Taquann system should speed up the whole body inhalation toxicity testing of the new nanomaterials and facilitate the process of categorization of manufactured nanomaterials using in vivo respiratory toxicity data. And, timely transfer of the toxicity data to the manufacturers and to the future users will contribute for the development and acceptance of the safe new products. (Supported by the Health and Labour Sciences Research Grant, MHLW, Japan).

Grouping of Nanomaterials by Release Type?

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ABSTRACT

Current assessments of possible exposures of workers, consumers, the population and the environment are mainly based on the direct measurements of nanomaterials (NM) in the corresponding exposure media. In cases where measurements are very tedious or near to impossible also models are applied to derive realistic exposure values. So we currently have the situation that a) measurements can be expensive, b) measurements are not really possible and models have to be applied, c) basic data on the release of NM are lacking for these models, and d) predictions of the likeliness of exposure are difficult to make without knowledge on possible release rates.

Hence basic developments and studies are currently on-going investigating release mechanisms and rates as well as the environmental transport. Additionally, national and international harmonisation and standardisation activities have started in recent years to facilitate the understanding and prediction of possible release.

One problem, immanent to nanomaterials is their high versatility with regard to the basic material and their modifications (e.g. morphology, surface functionality). It is near to impossible to test all NMs and their products for all possible scenarios. Hence, a grouping or categorization of NM and their product classes are needed. To allow a grouping some specific questions have to be tackled:

1) Which release mechanisms / processes can be differentiated and possibly used for grouping in view of release probabilities and rates?

2) How can the link from release (testing) to exposure be established and used for grouping of exposure scenarios? and

3) Which metric/particle parameter has to be used in view of sensitivity and possible impacts?

The presentation will deliver an overview of recent advancements and discuss suggested concepts.

Can a Grouping Approach Help Solve Some Key Nanomaterial Exposure Assessment Challenges?

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ABSTRACT

Meaningful exposure assessment is a critical element for accurate risk characterization and for the development of effective risk management strategies. Exposure to engineered nanomaterials can occur across a broad range of populations as the material

progresses down its life cycle. Human exposure can occur in researchers, manufacturing personnel, product consumers, and in the general population. The specifics of the exposure scenario will be dictated by a combination of the characteristics of the exposed group and of the nanomaterial itself. Logical groupings can be created for human exposure groups along the material and product life cycle. It should also be possible to approach the broad array of nanomaterials being introduced into commerce by grouping them into categories based on basic physical and chemical characteristic's. Creating a matrix made up exposed populations matched up with groupings of nanomaterils, weighted by parameters such as production volume and nature of the product using the nanomaterial will identify priority intersections where exposure assessment will be most meaningful. Moving this thinking into environmental exposure assessment will require a matrix of the environmental medium matched against many of the same characteristics used to group nanomaterils for human exposure. Additional factors such as agglomeration/deagglomeration, transformation, matrix degradation, and bioavailability will impact exposure assessment in both the human and environmental arenas, but will likely need to be addressed differently.

Session 2

Plenary Session on Risk Assessment: Utilization of Categories in Risk Assessment

Co-chairs: Yasir Sultan (Environment Canada, Canada) and Maila Poulamaa (European Commission, European Union)

Regulatory risk assessments (RA) involve addressing a combination of endpoints and exposure/release probabilities and frequencies to determine the level of risk to health or the environment[1] that a substance will present. The regulatory frame defines the (un)acceptable risk level. Factors to consider include, but are not limited to, identification, physical-chemical properties, fate in the environment, human health effects, environmental effects and exposure pathways to humans and environment. The risk assessment may cover a whole life cycle of the substance or selected parts and conclusions are made through balanced considerations of hazards and exposure. This framework holds true for both nano and non-nano substances Breakout session participants are invited to review the public OECD documents ENV/JM/MONO(2012)8[2] and follow-up prioritization in

[1] Chandler, R.; *BioEssays*, **1987**, *5*, 176.

[2] http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2012)8&doclanguage=en

ENV/JM/MONO(2013)18[3] for more context on ongoing *issues* specific to the risk assessments of nanomaterials.

The categorization of risks provides new means to better assess, manage and communicate them. Qualitative risk categories are useful in case of problems in measurability, while quantitative ones will provide higher degree of precision to the risk assessment and risk management measures. Independently from the methods used for categorisation of risks, their applicability areas and limitations should be defined as appropriate to enable a meaningful evaluation, management and communication.

For Nanomaterials RA, which in contrast to traditional chemical substances (non-nano) is still an emerging area, we have paucity of information and lacking experience – therefore uncertainties associated with almost every aspect of RA. Risk assessment practitioners continue to 'learn on the fly' and use 'innovative approaches' in the presence of ambiguous data, uncertainties and limited knowledge to make decisions.

One of the primary challenges for nanomaterials is that they offer an almost limitless variety[4] of combinations in terms of physical (size, shape, etc.) and chemical (surface, core, core-shell chemistries, etc.) properties. While scientists are developing all sorts of different types of nanomaterials, their properties and in turn behavior in different environments remain largely in the realm of the unknown. In addition, there is practically little to no information on the releases of nanomaterials and exposure pathways are very difficult to predict. As an interim approach, RA is conducted on nanomaterials on a substance-specific basis, i.e., data is generated on each nanomaterial. While generating substance-specific information is crucial, the usefulness of the data is limited since one cannot use the data to increase weight-of-evidence, use trend and statistical analysis to better risk conclusions and address RA gaps.

Over the past few years, there has been a steady increase in scientific literature suggesting ways to group nanomaterials into categories for the purposes of RA to aid in hazard and exposure determinations. Examples include works by:

- Kuempel et al. (2012)[5] on the development of categories for occupational exposure limits based on similar physical-chemical properties, biological mode of action, and comparative potency analysis;
- Madl et al. (2013)[6] who have suggested grouping for human health safety based on physical behavior including releasability from the matrix, exposure pathway, bioavailability, biopersistence and severity of health effects.

[3] http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2013)18&doclanguage=en

[4] Kuempel, E.; Castranova, V.; Geraci, C.; Schulte, P. *J. Nanopart. Res.*, **2012**, *14*, 1029.

[5] Kuempel, E.; Castranova, V.; Geraci, C.; Schulte, P. *J. Nanopart. Res.*, **2012**, *14*, 1029.

[6] Madl, A.K.; Unice, K.; Kreider, M.; Kovochich, M.; Bebenek, I.; Abramson, M. TechConnect World Conference, May 12-16, 2013. Washington DC. ISBN 978-1-4822-0586-2 Vol 3:485-488.

- Stone et al. (2010)[7], as part of the NanoImpactNet initiative, who identify a chemical-based categorization system as a 'reasonable starting point, with some modifications';
- Nel et al. (2013)[8] who have started to develop categories based on toxicological modes of action governed by physicochemical properties;
- Wang et al (2014)[9] on ranking and profiling bioactivity of a large number of diverse nanomaterials;
- Foss-Hansen et al. (2008) on the development of categories based on the location of the nanomaterial on/in the product[10] and recently, also categories of nanomaterial risks (NanoRiskCat)[11] for further ranking and communicating on nanomaterials;
- O'Brian et al. [2011][12] who developed a system for metallic nanomaterials of environmental concern in view of aquatic exposure and behavior;

In addition, Jahnel, Fleischer, and Seitz in 2013[13] authored a comprehensive review on the merits of different types of categorization schemes adapted from traditional approaches for evaluating risks of nanomaterials, including the Swiss Precautionary Matrix assessing risk and indicating risk management options[14].

Participants are expected to review the primary literature cited in this document and other works in literature prior to the workshop.

Plenary Session on Risk Management

Co-chairs: Maria Doa (Environmental Protection Agency, United States) and Henrik Laursen (European Union, European Union)
Rapporteur: Shaun Clancy (Product Regulatory Services, Business and Industry Advisory Committee)

The development of robust health and safety data for manufactured nanomaterials, an emerging area, is still in its initial stages. Assessments are further complicated because in addition to assessing the distinct species of manufactured nanomaterials, there must be a consideration of the related bulk chemical (if there is a related bulk chemical) and a

[7] Stone, V.; Nowack, B.; Baun, A.; Brink, N.; Kammer, F.; Dusinska, M.; Handy, R.; Hankin, S.; Hassollov M.; Joner, E.; Fernandes, T. *Sci. Tot. Env.*, **2010**, *408*, 1745.

[8] Nel, A.; Xia, T.; Meng, H.; Wang, X.; Lin, S.; Ji, Z.; Zhang, H. Acc. Chem. Res., 2013, 46, 607.

[9] Wang, A.; Berg, E.L.; Polokoff, M.; Yang, J., El-Badawy, A.; Reif, D. Kleinstreuer, N.; Marinakos,S.; Badireddy, A.R.; Gavett, S; Rotroff, D.; Gangwal, S.; Rabinowitz, J.; Matson, C.; Tolavmat, T.:, Mark Wiesner, M.; Houck, K. Poster, *Ranking and profiling nanomaterial (NM) bioactivity by ToxCast high-throughput screening (HTS)*, EPA (2014) http://www.epa.gov/ncct/download_files/sot/posters/2013/Wang%202013%20SOT%20Poster7.pdf

[10] Hansen, S. F.; Michelson, E.; Kamper, A.; Borling, P.; Stuer-Lauridsen, F.; Baun, A. Ecotoxicology, 2008, 17, 438.

[11] Hansen S.F.;Jensen K. A. ; Baun A. J Nanopart Res (2014) 16:2195

[12] O'BrianN.J; Cummins E.J. (2011); Risk Analysis, Vol. 31, No. 5, 2011

[13] Jahnel, J.; Fleischer, T.; Seitz, S. *2013*, **429,** 012063.

[14] Swiss Precautionary Matrix http://www.bag.admin.ch/nanotechnologie/12171/12174/index.html?lang=en

consideration of the distribution of materials (distinct species, agglomerates and aggregates). These factors and the gaps in health and safety data impact the precision of the assessments and thus the risk management tools that can be used. Further complicating risk management is that manufactured nanomaterials may be regulated under authorities more tailored to chemicals rather than manufactured materials. The lack of information (and thus a higher level of uncertainty), the complexity of manufactured nanomaterials, and the existing statutory frameworks may result in risk management decisions that may not be tailored appropriately for the material even though the hazard characterization, hazard assessment or risk assessment was conducted for individual manufactured nanomaterials. Thus, the risk management decision may be inconsistently insufficiently conservative or overly conservative. This session will provide background on the limitations regulators are dealing with in treating these complicated materials within a framework primarily established for chemicals.

Session 3 Physical-Chemical Characterization

Co-chairs: Vicki L. Colvin (Rice University, United States) and Angela Hight Walker (National Institute of Standards and Technology, United States)
Rapporteur: Scott Brown (DuPont Central Research & Development, Business and Industry Advisory Committee)

I. Introduction

Physical-chemical characterization of NPs is paramount in order to correlate biological/toxicological responses with these properties. The purpose of this session is to assess to what degree physical-chemical properties can or should be used to guide the categorization of manufactured nano-objects. Another goal is to ensure direct communication between the characterization and toxicology communities. The session will also identify guidance on necessary measurands and potential strategies to enable sufficiently thorough and proper physical chemical characterization of manufactured nano-objects.

II. Objectives of the Break-Out Session

a) Review relevant meetings outcomes and literature germane to the critical role of physical-chemical characterization in risk assessment.

b) Specific Issues to be addressed by the breakout session

Physical-chemical parameters collectively define how a nanomaterial will behave within a given system and therefore likely influence the environmental and human health impact of

nanomaterials. Since the properties of nanomaterials can influence their functionality, behavior and potential effects, physical-chemical characterization is inherently linked to all of the other break-out sessions.

The following questions will be addressed:

1) Thorough and proper physical-chemical characterization of nano-objects is a necessary step in order to properly interpret data from biological and environmental fate outcomes. Is there sufficient evidence to suggest that physical-chemical parameters can be used to predict or categorize manufactured nanomaterials based on the potential for biological or environmental impact? To what extent can physical chemical characterization be used to inform risk assessment or risk management?

2) Physical-Chemical characterization has the potential to encompass a vast number of tests that may or may not have relevance to a specific risk associated with a given manufactured nanomaterial. To what extent should physical-chemical parameters like composition be used to guide other "necessary" physical-chemical parameters? To what extent should fate & exposure or biological endpoints be integrated to assist in guiding physical-chemical analysis?

3) What physical-chemical endpoints are most applicable for accessing potential environmental impact? Potential human health impact? How do we ensure that the test regiments remain relevant despite the increasing complexity of materials and enhanced capabilities in terms of material design and synthesis?

4) What are their barriers to implementing detailed physical-chemical characterization into toxicology assessments, i.e. expense, availability, time, multidisciplinary nature?

5) Composition-based categorization schemes, such as the Proposed Strawman Categorization, provide a framework that lends itself to the development of specific physical-chemical test guidance based on a material's assigned category. This form of categorization attempts to simplify necessary testing based on bulk chemistry and integrates well with existing categorization paradigms. However, is the Proposed Strawman Categorization scheme a reasonable strategy for manufactured nanomaterials? Should Physical-Chemical parameters like composition lead categorization or should it support other schemes?

6) It is not always possible to directly compare physical-chemical characterization data from one study to another. To what extent is there a need to standardized test protocols, media and reference materials? How does one introduce a suitable amount of flexibility to ensure that the recommended procedures are valid within a given test substance? How to we ensure compliance with the recommendations?

7) How should physical-chemical testing be implemented? Is there a need for a tiered-approach integrating parallel biological/environmental endpoints?

Session 4 Environmental Fate Breakout Session

Co-chairs: Willie Peijnenburg (National Institute for Public Health and the Environment, The Netherlands) and Elijah Petersen (National Institute of Standards and Technology, United States)
Rapporteur: Steffi Friedrichs (Nanotechnology Industries Association, Business and Industry Advisory Committee)

The main issue of this breakout group will be to discuss the possibilities of grouping of nanomaterials with regard to their environmental fate. The discussion will be on the characteristics of groups of nanomaterials that determine the main processes that jointly determine the fate of a nanomaterial in water/soil/sediment. It is expected that as most information on these processes is available for the water compartment, the discussions on grouping will focus on this compartment.

Relevant endpoints
The environmental fate of nanomaterials is affected by the composition of the environment in terms of the physico-chemical composition of the environmental compartments, and the chemical and physico-chemical composition of the nanomaterial. In modelling and assessing the fate of a nanomaterials, it is common to use a bottom-up approach in which the basic processes/mechanisms are integrated in an overall fate model that is typically applicable to a specified class of chemicals. A schematic overview of the important fate processes for nanomaterials in the aquatic environment is given in Figure 1.

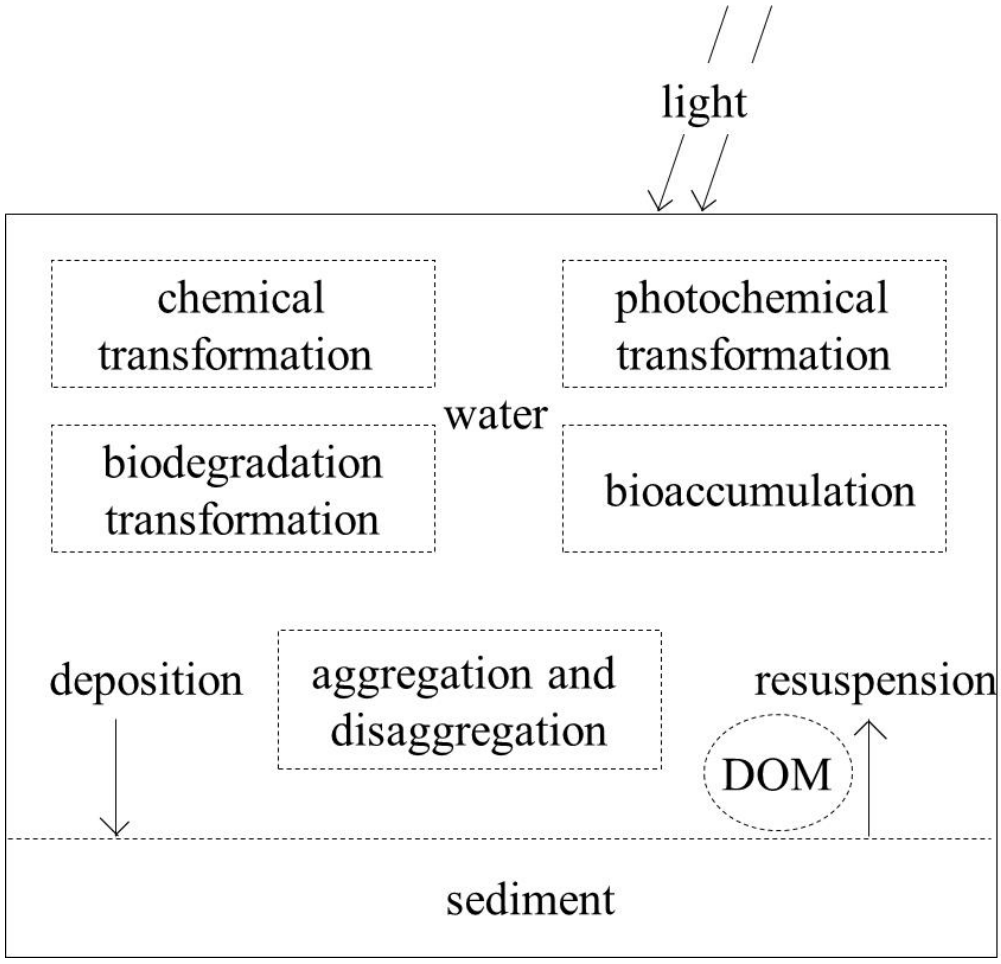


Figure 1. General overview of the main processes determining the fate of a nanoparticle in a stagnant aquatic environment.

As discussed by Baalousha et al. (2014) the main processes determining environmental fate, include:

- Aggregation/disaggregation
- Dissolution/precipitation
- (Bio)degradation
- Diffusion/sedimentation
- Nanoparticle coating, aging/weathering

The first issue of the breakout group will be on the completeness of this list of processes, taking account of differences among groups of nanomaterials.

Particle properties affecting environmental fate and factors of subcategories that impact multiple endpoint groups

The main part of the discussions within the breakout group will be on the nanoparticle properties that affect environmental behaviors for subcategories of nanomaterials and, vice versa, on the factors within subcategories of nanomaterials that impact the most important endpoints related to fate assessment. On the basis of the outcome of these discussions, appropriate types of testing for categories of nanomaterials and recommendations for grouping of nanomaterials with regard to environmental fate will be assessed.

The main goal of grouping of nanomaterials is to identify groups of nanomaterials that allow filling in data gaps by using information from other ('related') nanomaterials, subsequently providing guidance on what information is needed for actual read-across and for data-interpolation. As mechanism-based insight in the relationships between physico-chemical parameters and fate-determining processes is currently still in its infancy, the members of the breakout group are expected to discuss the best strategy for grouping of nanomaterials for this purpose. As such a distinction may be made between what is achievable in the near future and the way forward in the long run. An important consideration in this respect will be on the properties of nanomaterials that affect the various processes, such as the following:

- Charge
- Size
- Morphology
- Coating/natural corona
- Chemical composition
- …….

When combining the most important fate determining processes and general knowledge on particle composition, some potential categories of nanomaterials may be distinguished beforehand. For example:

- Dissolution is an important process with regard to the fate and the toxicity profiles of nanoparticles and could be substantial for some metallic nanoparticles like AgNPs, CuO NPs, but is less likely for AuNPs, TiO_2 NPs, and not applicable for carbon nanomaterials. In this respect, a strategy is needed for dealing with potential reformation of nanoparticles after dissolution, such as for AgNPs, taking account of new shapes that potentially may be formed.
- Biodegradation is only of potential relevance for carbon nanomaterials, although the coatings of other nanomaterials could also be degraded.
- We am not sure if there is sufficient information is available to begin grouping for other processes such as aggregation, sedimentation, bioaccumulation, etc. based on the nanomaterial properties.

Recommendations

The final part of the discussions is expected to focus on the best way forward in grouping of nanomaterials with regard to assessing their environmental fate.

References

- M. Baalousha, G. Cornelis, T. Kuhlbusch, I. Lynch, K. Nickel, W. Peijnenburg. Validation of model formulations for fate and behavior assessment of engineered nanomaterials. Environmental Science and Technology, in preparation, 2014.

Session 5 and 7 Human Health Breakout Sessions

Session 5
Co-chairs: Jenny Holmqvist (European Chemicals Agency, European Union) and Juergen Schnekenburger (Biomedical Technology Center of the Medical Faculty Münster, Germany)
Rapporteurs: Myriam Hill (Health Canada, Canada)

Session 7
Co-chairs: David Warheit (DuPont,Business and Industry Advisory Committee) and Phil Sayre (Environmental Protection Agency, United States)
Rapporteurs: Agnes Oomen (The National Institute for Public Health and the Environment, The Netherlands)

Nanogrouping or "Nanocategorization" is a concept (and a daunting task) that, going forward, will be critically necessary to implement as a framework in order to focus testing. To be specific, as new products containing manufactured nanomaterials come into commerce - it is unrealistic to assume that the safety profile of each of these individual components can be adequately tested or verified, for all of the relevant hazard endpoints in a timely manner. In theory, to implement this type of nanogrouping approach, closely related nanomaterials are assessed as a group or category, rather than as individual nanoparticulates so that not every manufactured nanomaterial-type would require individual testing for each of the relevant safety endpoints.

Implementing a framework for categorization that can be used in a regulatory context will be a complex process, due, in large part, 1) to the relative paucity of hazard information (for any relevant route of exposure) on many of the new manufactured-types; 2) insufficient information or criteria for assigning a particular manufactured nanomaterial-type to a particular group; 3) absence of relevant exposure information for the manufactured nanomaterial-type in question; 4) a variety of additional factors.

Where to begin? The development of functional categories (nanogrouping) for manufactured nanomaterials for the purposes of Read Across evaluations will require, at the outset, development of a trial and error approach and subsequent iterative process. The

similar chemistry represents the most commonly used approach for categorization, although in very specific cases the fiber paradigm may be also considered. As more information is developed, this process will inevitably be refined.

The human health breakout sessions will focus on addressing the following issues/questions:

- How can the *in vivo* hazard data/outcomes derived from the WPMN I Safety Testing Programme be systematically utilized/incorporated to develop a strategic pathway or general framework for implementing a nanocategorization programme.
- Representative manufactured nanomaterials were tested in the OECD Testing Programme. Can the results from these studies contribute to the database from which a nanocategorization process can be initiated?
- Given the relative paucity of hazard or exposure information on individual forthcoming/new manufactured nanomaterials, how can we commence a process or framework to ultimately use "Read-across" methodology for assessing the safety of manufactured nanomaterials?
- How similar or identical is the hazard or risk profile of the manufactured nanomaterials vs. the bulk materials of identical chemical composition? Many of the bulk materials have previously been safety tested or extensively evaluated – do they provide important clues on the hazards of manufactured nanomaterials for purposes of grouping?
- Can certain categories of manufactured nanomaterials with similar composition (*e.g.* metal oxides) be grouped for the purposes of hazard assessment via non-testing approaches (despite evidence some published data suggesting that certain forms of TiO_2 may have different pulmonary toxicity profiles?) Does this vary depending upon type of manufactured nanomaterials, *e.g.*, grouping may be more appropriate for subsets of CNTs?
- What are the minimum hazard information datasets necessary to adequately conduct hazard assessments via non-testing approaches? Are there any that can be done now?
- Given that, in general, there are different (*i.e.*, reduced) safety concerns associated with dermal and/or oral routes of exposure to manufactured nanomaterials relative to inhalation exposures of the same materials; can one separate the "Read-Across" processes to expedite the development of this framework for certain applications/anticipated exposure routes?
- Given the relevant paucity of *in vivo* hazard information on specific manufactured nanomaterials -types at relevant exposure concentrations (*i.e.*, to which humans will be exposed) and that some regulatory authorities continue to request *in vivo* testing given the limited alternatives -how can the those within the OECD encourage the initiation

and development of studies that address the impacts of manufactured nanomaterials exposures on a variety of endpoints in complex systems? Moreover, how can studies that can link *in vitro* studies to relevant *in vivo* findings be developed? What are the best ways to facilitate data sharing broadly? How can the *in vivo* testing that will continue to be generated in some jurisdictions be best used?

- How can a set of screening tools that reflect important characteristics or toxicity pathways for each of the relevant routes of exposure be developed? How can these tools provide important mechanistic data that can be utilized for non-testing approaches to hazard assessment? Important criteria for the experimental design of these studies include: for *in vivo* studies: robust physicochemical characterization of the manufactured nanomaterials of concern; relevant exposure/dose and appropriate dose-metrics; dose-response characteristics (*e.g.*, zinc-oxide particles); time course studies; benchmark controls for better interpretation of data;
- For transitioning of *in vivo* results to *in vitro* investigations, relevant cell types that reflect the appropriate route of exposure (oral, dermal, pulmonary – co-cultures vs. single-cell cultures; appropriate doses and dose metrics; dose-response characteristics; time-course studies; (critical) benchmark controls for necessary interpretation of hazard data.
- How should the proposed categorization be modified?

An important consideration in developing an approach will be on how the properties of nanomaterials affect various biological. The key physical-chemical parameters are:

- Particle size and size distribution (wet state) and surface area (dry state) in the relevant media being utilized – depending upon the route of exposure
- Crystal structure/crystallinity;
- Surface charge
- Agglomeration status in the relevant media;
- Surface functionalization/Composition/surface coatings;
- Surface reactivity;
- Dissolution/Solubility
- Method of nanomaterial synthesis and/or preparation including post-synthetic modifications (*e.g.*, neutralization of ultrafine TiO2 particle-types);
- Purity of sample

Do the results of the physical-chemical session result in changes to this group of physical-chemical parameters?

Breakout Session 1 will focus on an overview of the issue, purpose, use of sponsorship data, limitations and challenges of group. This session will discuss an overall approach. This session will also address the following issues.

- Define the purpose of the grouping/category
- Identify requirements for a regulatory decision
- Assessment and format of available data
- Minimum criteria for a scientific justification of the boundaries of the category/group

There are differences in what criteria should be considered and used to justify a decision on the possibilities to group and construct categories of nanomaterials and/or forms. However, despite these differences, it is recognised that a proper physical-chemical characterisation (structural similarities) is a fundamental start. Depending on the level of uncertainty, further information may be needed. In case of read-across to fill data gaps in a hazard characterisation of a substance, there is currently a need to strengthen the justification by also presenting toxicological data indicating similar behavior. A prelude to a read-across approach may be to examine the results of shorter-term test protocol results, in conjunction with results of standardized tests, in order to group materials and/or reduce further testing needs.

Breakout Session 1 will analyze the criteria, approaches and tools for manufactured nanomaterial categorization to allow for a combined evaluation of available categorization criteria. Breakout Session 1 has a focus on the data for different material properties and toxicological endpoints.

Following the discussion in Breakout Session 1, Breakout Session 2 will consider hazard endpoints in more detail, and attempt to build on the findings of Breakout Session 1. Presentations will focus on pulmonary toxicity and the construction of categories for relative toxicity evaluation. The working hypothesis is that physical-chemical properties alone will not be sufficient to build scientifically justified categorization of nanomaterials or forms of a certain nanomaterial. The questions to be addressed include:

- To what extent can categories be formed for pulmonary toxicity, based on (1) in vitro, and short-term in vivo, data; (2) physicochemical traits; and (3) other approaches such as mode-of-action groupings?
- How can these categories for pulmonary toxicity be used in reduced testing and/or read across contexts?

- How can similar approaches to reduce testing needs be used for other health endpoints?

Session 6 Environmental Toxicity Breakout Session

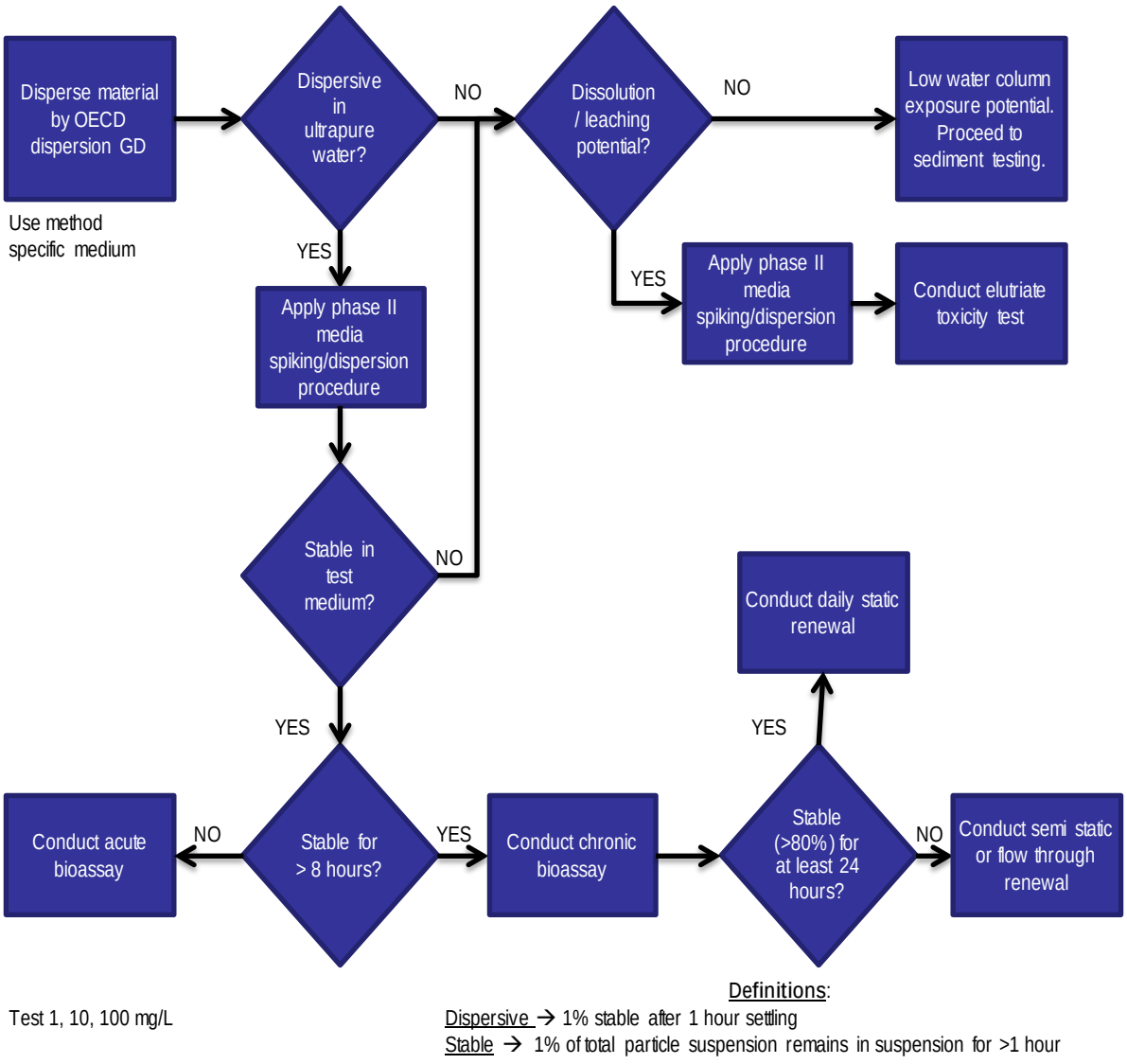
Chair: Greg Goss (University of Alberta, Canada). Rapporteur: Eric Bleeker (The National Institute for Public Health and the Environment, The Netherlands)

Breakout group on environmental toxicology
This breakout group will focus on the grouping of nanomaterials with regard to their ecotoxicological effects. The discussion will be on the characteristics of groups of nanomaterials that jointly determine the environmental toxicity of a nanomaterial towards aquatic, terrestrial and sediment species. Similar to non-nanomaterials it can be expected that for risk assessment the main focus will be on aquatic ecotoxicology and thus this will form an important part of the discussions in this breakout group. In addition this breakout will benefit from the discussion on environmental fate and grouping of nanomaterials as the environmental toxicity of materials will in part be determined by their fate, both in the environment and in the test system.

Aquatic endpoints
During the OECD Expert Meeting on Ecotoxicology and Environmental Fate in Berlin (January 2013) it became apparent that knowledge on particle behavior in test media is still limited. Nevertheless it was concluded that dissolution and dispersability are important processes, which resulted in the recommendation from this workshop to develop (guidance for) a decision tree that helps in decision towards the most relevant ecotoxicity testing (e.g. aquatic, sediment, or terrestrial testing).
Work on such a decision tree has started, including an Expert Workshop on the "Guidance Document on Aquatic (and Sediment) Toxicology Testing of Nanomaterials" that was held in Washington in July 2014. A presentation on this workshop will be given along with the key findings and discussion points from that workshop. The key goals of the workshop were to define as best as possible uniform and consistent bioassay data to inform future test guidelines and risk decisions, partly building on the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures. Four phases were identified that need further guidance:

1. The generation of a particle stock medium, needed for spiking test media (this should meet certain dispersion / stability criteria that need to be defined);
2. The production of exposure media and dosing method (optimization is needed that takes into account particle stability and organism health);
3. The conduction of the assay itself (which needs identification of acceptable methods, including monitoring frequency);
4. The analysis and reporting of the data (which may need guidance on interpretation and dosimetry).

Each of these steps may inform potential possibilities for grouping nanomaterials as well.
The workshop in July decided on a preliminary decision tree for a priori decisions of how to conduct tests and which tests are needed to conduct (Figure 1). To some extent similar questions may lead to grouping of the nanomaterials.
The usefulness of such an approach for grouping of nanomaterials will be further discussed.



Terrestrial endpoints

The second part of the discussion will focus on environmental toxicity tests with terrestrial organisms. In the complex soil compartment toxicity is even more

influenced by availability of the nanomaterials and thus the discussions on environmental fate will be important for these endpoints as well. Nevertheless, specific modes of action (e.g. ion release) may be of influence in determining the most influential factors determining terrestrial toxicity, thus informing potential parameters for grouping of nanomaterials.

Recommendations

The final part of the discussions is expected to focus on the best way forward in grouping of nanomaterials with regard to assessing their toxicity in the different environmental compartments water, sediment and soil.

Session 8 Exposure Assessment

Chair: Vladimir Murashov (National Institute for Occupational Safety and Health, United States);
Rapporteur: Kim Rogers (Environmental Protection Agency, United States)

Engineered Nanomaterials (ENMs) are considered separately from their bulk elemental or compound forms primarily because of their size which endows them with unique physical and chemical properties (i.e., <100 nm in one dimension [plates], in two dimensions [fibers and tubes] or in three dimensions [particles]). Specifically, ENMs have a very high surface area per unit mass, as well as unique optical, electrochemical and chemical reactivity that can vary significantly with the size, shape and surface coatings even for particles of essentially the same core elemental composition. These characteristics present a significant challenge for categorizing ENMs with respect to their potential for human and ecosystem exposure.

Although occupational exposure through the inhalation pathway is likely to produce the most significant exposures and potential hazard, a wider range of potential human and environmental exposures should be considered. A more comprehensive approach becomes particularly relevant as ENM-enabled products and processes increase in scope, number of product types and total production volumes. One way to view this challenge is to consider the exposure potential for specific types of particles from manufacture to final disposition. A potential advantage to a lifecycle approach is that it may provide a more comprehensive treatment required by regulators who are routinely petitioned to provide risk analyses for specific particle types proposed for specific industrial or consumer-based applications. In addition to occupational exposures during manufacture and formulation, this approach may also direct attention to potential human exposures and environmental contamination that may occur during use, disposal / recycle and final disposition which have not always been considered by manufactures. Figure 1

represents a schematic framework that may begin a discussion concerning a lifecycle approach to exposure assessment of ENMs.

One of the charges for the Exposure Assessment Breakout Group is to provide recommendations for categorization of nanomaterials based on exposure assessment considerations which is an integral part of the assessment and management of risk. Risk analysis for ENMs requires information concerning physicochemical properties, hazard and exposure as well as a clear understanding of how features and events from these areas interact with each other (Stone et al., 2014). ENM physicochemical characteristics and their effect on exposure to target organisms together contribute to risk. The influence of both ENM characteristic and exposure scenarios on risk (to both humans and ecosystems) exist along separate continua. As a simplistic example, a highly hazardous type of ENM may rarely encounter a target organism, or by contrast, a target organism may be chronically exposed to an ENM that shows only a moderate acute biological response. In any case, risk assessment must include contributions from physicochemical properties, hazard and exposure.

A wide range of physicochemical properties have been used to characterize ENMs for a diverse range of endpoint requirements. With respect to ENM exposures, certain physicochemical characteristics tend to be more influential than others (Kuempel et al., 2012). For example, dustiness, defined as the propensity of a material to generate airborne dust during its handling, is one of the determinants of exposure and re-suspension potential of a nanomaterial. Dustiness is not an inherent ENM characteristic and can vary considerably depending on environmental conditions such as humidity. It can, however, be assessed using standardized techniques (Evans et al 2013). Similarly, in the liquid media, one of characteristics that influences environmental fate and transport and resulting environmental exposure potential is the ease of nanomaterial dispersal. This feature is also dependent on multiple inherent properties such as particle size distribution, surface charge and surface potential (Hendren et al 2013). For example, there are a number of indicators of exposure related to manufacturing processes and consumer product use that are largely independent from physicochemical and toxicological characteristics (Figure 2) (Hristozov et al., 2014, Clark et al., 2012). Also, in the case of exposures related to consumer products or industrial processes, the physicochemical properties of the matrix may also become an important consideration (Clark et al., 2012). This is particularly important for ENMs that are dispersed in food or personal care products; embedded into polymers used to construct various rubber, plastic or glass products; coated onto surfaces such as textiles; or used for industrial or professional products such as exterior coatings for buildings or added to concrete.

It is our hope that these ideas may help to focus the following expected outcomes.

Expected outcomes: 1) Recommendations for considerations in worker exposure assessments among categories; 2) Factors of subcategories (e.g., category of

nanomaterial, size, coating/surface functionalization) that may impact multiple endpoint groups; 3) Recommendations for considerations in environmental exposure assessments among categories); 4) Identification of scientific gaps and further areas for focus; 5) Recommendations for changes to strawman categories grouping

References:

Clark, K., van Tongeren, M., Christensen, F.M., Brouwer, D., Nowack, B., Gottschalk, F., Micheletti, C., Schmid, K., Gerritsen, R., Aitken, R., Vaquero, C., Gkanis, V., Housiadas, C., Lopez de Ipina, J.M., Riediker, M. Limitations and information needs for engineered nanomaterial-specific exposure estimation and scenarios: recommendations for improved reporting practices. J. Nanopart. Res. 14 (2012) 970.

Evans, D.E., Turkevich, L.A., Roettgers, C.T., Deye, G.J., Baron, P.A. Dustiness of Fine and Nanoscale Powders. Ann. Occup. Hyg. 57 (2013) 261-277.

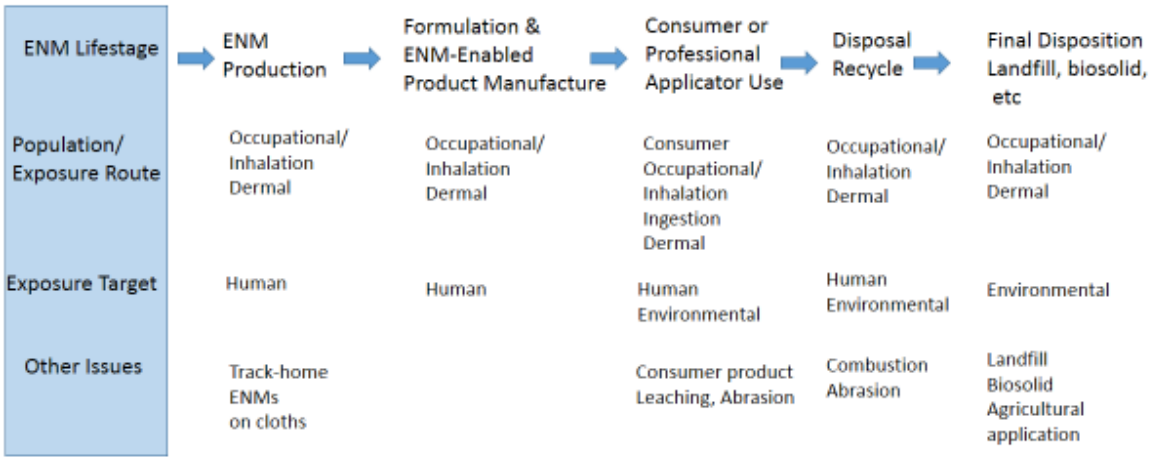
Hendren C.O., Lowry, M., Grieger, K.D., Money, E.S., Johnston, J.M., Wiesner, M.R., Beaulieu, S.M. Modeling Approaches for Characterizingand Evaluating Environmental Exposure to Engineered Nanomaterials in Support of Risk-Based Decision Making. Environ. Sci. Technol. 47 (2013) 1190-1205.

Hristozov, D.R., Gottardo, S., Cinnelli, M., Isigonis, P., Zabeo, A., Critto, A., van Tongren, M., Tran, L., Marcomini, A. Application of a quantitative weight of evidence approach for ranking and prioritizing occupational exposure scenarios for titanium dioxide and carbon nanomaterials. Nanotechnol. 8 (2014) 117.

Kuempel, E.D., Castranova, V., Geraci, C.L. Development of risk-based nanomaterial groups for occupational exposure control. J. Nanopart. Res. 14 (2012) 1029.

Stone, V., Pozzi-Mucelli, S., Tran, L., Aschberger, K., Sabella, S., Vogel, U., Poland, C., Balharry, D., Fernandes, T., Gottardo, S., Hankin, S., Hartl, M.GJ., Hartmann, N., Hristozov, D., Hund-Rinke, K., Johnston, H., Marcomini, A., Panzer, O., Roncato, D., Saber, A.T., Wallin, Hakan, Scott-Fordsmand, J.J. ITS-NANO-Prioritizing nanosafety research to develop a stakeholder driven intelligent testing strategy. Particle Fibre Toxicol. 11 (2014) 9.

Framework for Exposure Assessment Based on ENM Lifecycle



Exposure-relevant ENM / Process Characteristics

(Adapted from Hristozov et al., 2014)

- **Physicochemical Characteristics**
  - Dustiness, Size (distribution), Shape, Surface area, Surface charge, Surface coating, Reactivity, Solubility-Dissolution
- **Manufacturing Process Features**
  - Physical Environment, Weight-fraction, Duration of handling,
  - Automatic processing, Ventilation, Respiratory protection
- **Consumer Product**
  - Use-dependent exposure route, Leaching of ENM or Ions from matrix,
  - Use by vulnerable populations
- **Ecosystem Issues**
  - Entry point into Ecosystem, Frequency and amount of release, Transport Potential Transformation of ENM in Environment, Vulnerable indicator species

Session 9 Risk Assessment

Chair: Yasir Sultan (Environment Canada, Canada); Rapporteur: Kirsten Rasmussen (European Commission Joint Research Centre, European Union)

The purpose of this breakout session is to discuss the merits and purpose of the different types of categorization schemes listed above and those available in literature, identify commonalities and differences between these schemes, agree on which are the most appropriate for specific application domains and closest in terms of maturity for use in RA of nanomaterials, and their applicability domain i.e., where in the nanomaterials risk assessment process an approach/scheme has already been used or can be used to increase weight-of-evidence and reduce uncertainties. The discussion will not be limited to using categorization schemes to inform hazards, but rather how a more balanced risk determination can be made by increasing knowledge on both hazards and exposure through categories. In addition to identifying gaps associated with using these categorization schemes for nanomaterials RA, participants will be asked to identify how to address the gaps, i.e., through the development of test guidelines and/or guidance, engagement with ongoing scientific collaborations/activities, or new research directions. Breakout session chairs will provide a brief overview of relevant categorization schemes at the workshop but participants will be expected to prepare beforehand.

The session will have stimulus presentations from co-authors of primary literature. Participants should come prepared to critically evaluate the existing schemes or provide insights into the development of new ones. Following the stimulus presentations, there will be a discussion amongst participants followed by a panel discussion of key experts to try and generate consensus.

Outcomes from this session should include a prioritization of categorization schemes, i.e., which ones are the most appropriate for nanomaterials RA and are the closest to being mature. Follow-up work will be recommended to the OECD WPMN steering group on risk assessment and regulatory programs (SG-AP) and interested experts to further integrate these schemes into the RA process.

Lastly, it is suggested that the conclusions will form the basis for the preparation of a publication in peer-reviewed literature summarizing the discussion of the break-out session and the possibly identified path forward.